Conferences and Reviews

Congestive Heart Failure
New Frontiers

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Congestive heart failure is a common syndrome with high mortality in its advanced stages. Current therapy includes the use of vasodilator drugs, which have been shown to prolong life. Despite current therapy, mortality remains high in patients with severe heart failure. Potent new inotropic vasodilators have improved ventricular performance but have not prolonged life in patients with end-stage heart failure. Serious arrhythmias are implicated in the sudden deaths of 30% to 40% of patients with severe heart failure, but the benefits of antiarrhythmic therapy have not been established. Upcoming trials will address this question. Ventricular remodeling and progressive dilatation after myocardial infarction commonly lead to congestive heart failure; early unloading of the ventricle with an angiotensin-converting enzyme inhibitor may attenuate these events. These findings support the concept that angiotensin-converting enzyme inhibitors may be useful in managing heart failure of all degrees of severity, including left ventricular dysfunction and end-stage heart failure. Part of the damage that may occur with acute myocardial infarction, particularly in this era of thrombolysis therapy, is reperfusion injury, which may be mediated by oxygen-derived free radicals. Better knowledge of the mechanisms and treatment of myocardial infarction, the leading cause of congestive heart failure, may help prevent or attenuate the development of this syndrome.

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WILLIAM W. PARMLEY, MD*: Each year, congestive heart failure, a syndrome affecting about 3 million persons or about 1% of the population, develops in about 400,000 Americans.[1] By age 75, the prevalence of this syndrome rises to about 10%. Congestive heart failure is now the most common hospital discharge diagnosis among patients older than 65 years. Over the past several years, the incidence and prevalence of this syndrome appear to have increased while mortality from cardiovascular diseases has progressively declined. This presumably reflects the fact that more people are living to ages when congestive heart failure becomes more prevalent.

In the Framingham study, five-year mortality after congestive heart failure developed was about 60% in men and 45% in women.[2] Currently about 50% of patients with class IV heart failure (symptoms at rest) die within a year. Death is sudden in about 40% of patients, indicating that severe arrhythmias also play an important role.[3]

Current therapy for congestive heart failure includes several steps, as outlined in Table 1. First, the cause of the heart failure should be determined to set the stage for appropriate therapy. Second, the relative importance of diastolic dysfunction must be evaluated. If this dysfunction is the primary pathophysiology, therapy must be chosen accordingly. Third, appropriate surgical correction should also be considered. This may include valve replacement to treat pressure or volume overload or revascularization procedures to treat severe widespread ischemia contributing to the heart failure. Fourth, nonpharmacologic approaches, such as reducing salt intake and physical and emotional stress, should be considered. Nonpharmacologic approaches usually do not produce major changes in the degree of heart failure but may offer some benefit.

Fifth, pharmacologic therapy should be considered. Recent data suggest that the use of diuretics, digoxin, or vasodilators can be considered as first-line therapy and that combining these three classes produces maximal hemodynamic effects.[4-6] Depending on the first agent chosen, either or both of the other two classes of drugs may be added as necessary. Because vasodilators have prolonged life in patients with moderate[4] to severe[5] heart failure, their use should be considered for all forms of congestive heart failure. If these agents produce insufficient hemodynamic benefits, the potent new inotropic agents should be considered.[7] For patients with dilated cardiomyopathy, some data suggest that administering β-blockers like low-dose metoprolol may produce some

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ABBREVIATIONS USED IN TEXT

cAMP = cyclic adenosine monophosphate
ISIS-2 = Second International Study of Infarct Survival

benefit.[8] The patient group likely to benefit most from this approach has not yet been identified but may include those with excess tachycardia. Antiarrhythmic therapy is of uncertain benefit.[9] In view of this uncertainty, it is at least reasonable to attempt to reduce such proarrhythmic factors as electrolyte imbalance and ischemia and to avoid the use of potent inotropic agents when possible.

Finally, if all these measures are inadequate, heart transplant should be considered for appropriate patients. Transplant patients have a dramatic reduction in mortality compared with the pool of patients with end-stage heart failure from which they are selected.[10] More important, transplants improve the quality of life considerably. A limited availability of donor hearts restricts transplant candidates to patients meeting general criteria, including terminal heart disease; no diabetes mellitus or other systemic disease; age younger than 55 to 65; good renal, pulmonary, and hepatic function; no active infection or ulcer disease; no pulmonary hypertension or severe peripheral vascular disease; and psychosocial stability.[10]

Despite these demonstrated benefits of conventional therapy for congestive heart failure, many new frontiers remain to be explored. This conference explores four important current questions regarding the management of congestive heart failure. In the first section, Kanu Chatterjee, MD, considers the value of the potent new positive inotropic agents and their potential for doing harm. In the second section, Gary Francis, MD, explores the problem of sudden death in patients with severe congestive heart failure. Do antiarrhythmic agents or other interventions have any place in the care of these patients? In the third section, Brian Firth, MD, discusses the importance of attenuating the development of congestive heart failure following myocardial infarction. Can vasodilator therapy with angiotensin-converting enzyme inhibitors prevent the dilatation and remodeling that occur after myocardial infarction and that then lead to end-stage heart failure? In the fourth section, Robert Kloner, MD, in collaboration with Karin Przyklenk, MD, discusses an important issue in the thrombolytic era—whether reperfusion damage to the heart can be limited following successful thrombolytic therapy in acute myocardial infarction. A better understanding of these four issues will clearly influence our future approach to patients with congestive heart failure.

TABLE 1.—*Steps in the Management of Congestive Heart Failure*

Determine cause
Evaluate importance of diastolic dysfunction
Correct surgically, where possible
Nonpharmacologic therapy
Restrict salt intake
Reduce physical and emotional stress
Pharmacologic therapy
Begin with vasodilator, diuretic, or digoxin
Add other 2 as necessary
Special considerations
β-Blocker for dilated cardiomyopathy
Antiarrhythmic therapy
Heart transplant, if appropriate and feasible

Promise and Problems of New Inotropic Agents

KANU CHATTERJEE, MB, FRCP*: The pharmacotherapeutic management of congestive heart failure has progressed considerably in the past two decades. Whereas diuretics and digitalis were the only drugs available for many years, vasodilators, including angiotensin-converting enzyme inhibitors, have now been added to the armamentarium. Vasodilators, especially angiotensin-converting enzyme inhibitors, have been shown to improve the prognosis of patients with moderate[4] to severe[5] congestive heart failure and should always be considered for the management of these patients.

Mortality, however, remains high in the sizable proportion of patients who fail to respond or become refractory to vasodilator therapy. In addition, unacceptable complications develop in some patients or they cannot tolerate vasodilators or angiotensin-converting enzyme inhibitors. Thus, the search continues for new therapeutic strategies and pharmacologic agents, including inotropic drugs. In this section I describe newer nonglycosidic inotropic drugs in clinical use or undergoing clinical trials in patients with heart failure.

Classification and Mechanisms of Action of Nonglycosidic Inotropic Drugs

The primary mechanism for increased contractility is increased intracellular calcium concentration or increased responsiveness of myofilaments to calcium. The two broad categories of nonglycosidic inotropic drugs, adrenergic and nonadrenergic agents, modulate calcium concentration and sensitivity by different mechanisms. Adrenergic agents include dopamine, dobutamine, dopexamine, propylbutyldopamine, bromocriptine, fenoldopam, ibopamine, levodopa, butopamine, denopamine, colforsin (forskolin), pirbuterol, albuterol (salbutamol), and xamoterol. Nonadrenergic agents include amrinone, enoximone, imazodan (CI-914), milrinone, pimobendan, piroximone, sulmazole, vesnarinone (OPC-8212), VD-CA 115, and VD-CA 212.

Mechanisms of Action of Adrenergic Agents

The pharmacophysiologic effects of the adrenergic agents result from an activation of the various subtypes of adrenoreceptors.

β-Adrenoreceptors. The activation of myocardial β_1-adrenoreceptors, which stimulates the adenylate cyclase-cyclic adenosine monophosphate (cAMP) system and promotes calcium influx, is associated with increased contractility.[11] Cardiac cAMP production can be increased by activating the catalytic unit of the adenylate cyclase system without stimulating β_1-receptors. This appears to be the primary mechanism of action of some adrenergic inotropic drugs such as colforsin.[12] The activation of non-β-receptors, such as glucagon receptors, is also associated with increased cAMP production.

Studies indicate that the activation of the β_2-receptors found in human myocardium results in cAMP production and increased contractility,[13] but β_2-receptor agonists also stimulate β_2-receptors in peripheral vascular beds and induce peripheral vasodilatation. Activation of the β_2-receptors found on prejunctional nerve terminals facilitates the release of neurotransmitters[14] and may also contribute to peripheral

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vasodilatation. Thus, β_2-receptor agonists have the potential to enhance contractility and decrease left ventricular afterload.

α-Adrenoreceptors. The activation of myocardial α_1-adrenergic receptors is also associated with enhanced contractility,[15] but such stimulation does not increase adenylate cyclase activity. It has been proposed that alterations in the polyphosphoinositide second-messenger system may mediate the action of myocardial α-receptors. At present, the existence and relevance of α_1-receptors in human myocardium remain uncertain. Furthermore, currently available adrenergic agonists also activate peripheral α-receptors. The activation of α_1-receptors in postganglionic effector cells is associated with a contraction of vascular and nonvascular smooth muscles.[16] The stimulation of α_2-receptors inhibits neuronal release of the neurotransmitters, and the activation of postjunctional α_2-receptors induces vasoconstriction.[17] Thus, the clinical use of α-agonists is limited to the treatment of hypotension.

Dopamine receptors. Two subtypes of dopamine receptors have been recognized.[18] The activation of dopamine$_1$ receptors is associated with the dilatation of renal, mesenteric, coronary, and cerebral vascular beds. The stimulation of dopamine$_2$ receptors on postganglionic sympathetic nerves and autonomic ganglia inhibits norepinephrine release from sympathetic nerve endings. Thus, the activation of dopamine receptors produces peripheral vasodilatation but does not directly influence contractile function.

Mechanisms of Action of Phosphodiesterase Inhibitors

The inhibition of cardiospecific (FIII) phosphodiesterase is the principal mechanism of action of nonadrenergic inotropic agents such as amrinone, milrinone, and enoximone. Intracellular phosphodiesterases are necessary for cAMP degradation, and their inhibition increases intracellular cAMP concentrations and contractility. Furthermore, the inhibition of phosphoprotein phosphatases, the enzymes required for the dephosphorylation of phosphorylated proteins, produces effects similar to those of increased cAMP. An increased affinity of contractile elements for calcium also enhances contractility; this has been proposed as the principal mode of action of new inotropic agents such as pimobendan and sulmazole.[19]

Mechanism of Action of Glycosidic Inotropic Drugs

The inhibition of surface-bound "sodium pump" is associated with transient increases in intracellular calcium concentrations due to increased sodium influx and activation of the sodium-calcium exchange. This is the proposed mechanism of action of digitalis glycosides.[20]

Systemic Hemodynamic Effects and Changes in Cardiac Performance

Most adrenergic inotropic drugs concurrently stimulate several subtypes of myocardial and peripheral adrenoreceptors, and their net effects are determined by the relative dominance of the receptors stimulated. The activation of myocardial β_1, β_2, and dopamine receptors increases contractility and improves cardiac performance. The stimulation of peripheral β_2 and dopamine receptors is associated with lower systemic vascular resistance and arterial pressure, which decrease left ventricular ejection impedance and improve left ventricular performance. Peripheral vasoconstriction and increased systemic vascular resistance and arterial pressure result from the activation of peripheral α-adrenoreceptors, which also increase left ventricular outflow resistance. Thus, the stimulation of peripheral α-adrenoreceptors may reduce stroke volume and cardiac output and cause deterioration of left ventricular function. Table 2 summarizes the expected systemic hemodynamic effects of newer adrenergic inotropic drugs.

Dopamine and Related Agents

Dopamine hydrochloride and dobutamine hydrochloride. These agents, the two most frequently used parenteral adrenergic inotropic drugs, exhibit some therapeutically relevant differences in hemodynamic effects. In general, each increases cardiac output, but dopamine causes the pulmonary capillary wedge pressure to remain the same or even increase, whereas dobutamine causes it to decrease in most patients.[21] Large doses of dopamine may increase total systemic and pulmonary resistance as well as systemic and pulmonary arterial pressure, thereby increasing the ejection impedance and causing no further increase, or even a decrease, in cardiac output. With dobutamine use, systemic vascular resistance decreases, cardiac output increases, and the mean arterial pressure remains unchanged or even falls. Thus, when the primary objective is to increase arterial pressures in hypotensive patients, the use of dopamine is preferable to that of dobutamine. Using dobutamine is preferable to using dopamine in patients with low cardiac output, adequate arterial pressure, and elevated pulmonary capillary wedge pressure.

Dobutamine therapy also effectively increases systemic output in patients with acute right ventricular failure complicating right ventricular infarction.[22] It has been shown to be more effective than digoxin in improving left ventricular function when given to patients with acute myocardial infarction.[23] When an inotropic agent is necessary for the treatment of acute pump failure, dobutamine is preferable because it acts faster than digoxin.

Newer dopaminergic agents. The systemic hemodynamic effects of newer dopaminergic agents are similar to those of dopamine, but their relative advantages in managing heart failure remain to be established. Dopexamine hydrochloride, an intravenous, short-acting agent, appears to have β_2- and dopamine$_1$-receptor agonist activity. It increases cardiac output and stroke volume while decreasing right atrial and pulmonary capillary wedge pressures.[24] Parenteral propylbutyldopamine has both dopamine$_1$- and dopamine$_2$-receptor agonist activity.[25] Bromocriptine has dopamine$_2$-receptor agonist activity in peripheral vascular beds and decreases sympathetic activity by a central nervous system mechanism.[26] Fenoldopam is a selective dopamine$_1$-receptor agonist.[27]

Ibopamine. This dopamine analogue undergoes hydrolysis to epinine (*N*-methyldopamine) by esterase hydrolase. An orally active drug, it exerts both inotropic and vasodilating effects. Ibopamine appears to activate vascular α_1-adrenoreceptors, β-adrenoreceptors, and dopamine receptors. It increases cardiac output, stroke volume, and stroke work indexes without reflex alterations in heart rate or in mean arterial, systemic, and pulmonary venous pressures. Transient increases in right atrial and pulmonary capillary wedge pressures and in total pulmonary resistance have also been observed.[28]

Levodopa. This pro-drug is converted to dopamine by aromatic amino acid decarboxylase in the liver and other

tissues. Blood concentrations of levodopa and dopamine peak one to three hours after oral administration. Following an oral dose of 1.5 to 2.0 grams of levodopa, systemic hemodynamic effects are similar to those of an infusion of 2.0 to 4.0 μg per kilogram per minute of dopamine. Cardiac output usually increases modestly, without a substantial change in heart rate, blood pressure, or pulmonary capillary wedge pressure, but systemic vascular resistance decreases.[29]

Butopamine. This synthetic sympathomimetic amine is similar to dobutamine except that its resistance to *O*-methylation permits oral administration. Although butopamine exerts a positive inotropic effect, it may produce undesirable, excessive tachycardia.[30]

Denopamine. Another β-receptor agonist, denopamine reportedly produces systemic hemodynamic effects similar to those of butopamine.[31]

Bronchodilators

Albuterol and pirbuterol acetate are primarily β_2-receptor agonists, although they may exhibit ancillary β_1-adrenoreceptor stimulation. The systemic hemodynamic effects of albuterol consist of increased cardiac output, a modestly increased heart rate, and decreased pulmonary capillary wedge pressure and systemic vascular resistance.[32] The systemic hemodynamic effects of pirbuterol are similar to those of albuterol,[33] but undesirable tachycardia has occurred particularly after intravenous administration.

Partial β-Receptor Agonists

A new approach to the inotropic treatment of heart failure has emerged with the development of partial β_1-receptor agonists. These partial agonists cause less than the full physiologic response when all receptors are occupied. On the other hand, full agonists stimulate the full physiologic response when all receptors are occupied, and their physiologic effects are totally inhibited by full antagonists. The pharmacologic rationale for using partial agonists is that their intrinsic sympathomimetic activity exerts a positive but not excessive inotropic effect. Moreover, partial agonists may also attenuate the adverse effects of elevated catecholamine levels.

Prenalterol hydrochloride. This partial β-receptor agonist has 70% to 80% of the sympathomimetic activity of isoprenaline.[34] Prenalterol substantially increases cardiac output and decreases pulmonary capillary wedge pressure and systemic vascular resistance with little or no change in arterial pressure or heart rate.

Xamoterol. In contrast to prenalterol, this selective β_1-receptor agonist has only about 43% of the inotropic and chronotropic activity of isoprenaline. It does not appear to have any significant β_2-adrenoreceptor-agonist activity. Although xamoterol use usually does not produce any immediate beneficial hemodynamic effects in patients with severe heart failure,[35] it does appear to benefit patients with mild to moderate heart failure. The lack of benefit in patients with severe heart failure may relate to the markedly increased sympathetic tone and decreased myocardial β-receptor density usually observed in these patients.

Phosphodiesterase Inhibitors

Although phosphodiesterase inhibitors are structurally dissimilar to each other and to methylxanthines, they exhibit similar pharmacologic properties and systemic hemodynamic effects.[7,36-39] The hemodynamic effects include substantial increases in cardiac output, stroke volume, and stroke work and decreases in systemic and pulmonary venous pressures with little or no change in heart rate or mean arterial pressure. With large doses of phosphodiesterase inhibitors, tachycardia and hypotension may develop.

Positive inotropic effects of phosphodiesterase inhibitors have been documented by various methods. The intra-

TABLE 2.—*Hemodynamic Effects of Selected Adrenergic Inotropic Drugs*

	Receptor Activation			Hemodynamic Effects				
Drug	α	β_1	β_2	*SVR*	*Mean BP*	*Cardiac Output*	*Heart Rate*	*PCWP*
Dopamine HCl*	+++	++	–	↓↔	↑↑	↑↑	↑	↑↔
Dobutamine HCl	+	+++	+	↓	↔↓	↑↑↑	↔↑	↓↔
Albuterol	–	+	+++	↓↓	↓↔	↑↑	↔↑	↓↔
Pirbuterol acetate	–	+	+++	↓↓	↓↔	↑↑	↔↑	↓↔
Prenalterol HCl	–	++	–	↓	↔↓	↑	↔↓	↓↔
Xamoterol	–	+	–	↔↓	↔↓	↑	↔↓	↑↔
Levodopa*	+	+	+	↓	↔	↑	↔↑	↔
Ibopamine*	–	+	+	↓	↔	↑	↑↔	↑↔
Dopexamine HCl†	–	+	+	↓	↔	↑	↑↔	↑↔

BP = blood pressure, HCl = hydrochloride, PCWP = pulmonary capillary wedge pressure, SVR = systemic vascular pressure, + = activation, – = no effect, ↑ = increase, ↓ = decrease, ↔ = no change

*Also activates dopamine$_1$ and dopamine$_2$ receptors.
†Acts as a dopamine$_1$-receptor agonist.

TABLE 3.—*Potential Indications for Nonglycosidic Inotropic Therapy*

Intravenous	*Nonparenteral*
Acute heart failure with hypotension	Failure of vasodilators or ACE inhibitors
Acute exacerbation of chronic heart failure with hypotension	Intolerance to vasodilators or ACE inhibitors
In combination with vasodilators	In combination with vasodilators or ACE inhibitors
"Low output state" after a cardiac operation	Refractory heart failure, awaiting cardiac transplantation
Septic shock	
Intermittent infusion in chronic refractory heart failure	

ACE = angiotensin-converting enzyme

coronary infusion of low doses of milrinone did not produce any important systemic hemodynamic effects but did increase left ventricular dp/dt (rate of the rise of pressure), suggesting enhanced contractility.[36] Enoximone, another phosphodiesterase inhibitor but structurally different from milrinone, also exerts direct positive inotropic effects.[37] In addition to enhancing contractility and decreasing afterload, phosphodiesterase inhibitors may improve left ventricular function by increasing left ventricular distensibility.[40] The mechanism for improved left ventricular diastolic compliance, however, remains unclear. Nevertheless, phosphodiesterase inhibitors may enhance cardiac performance by several mechanisms.

Influence of Inotropic Agents on Myocardial Oxygen Consumption

The adrenergic inotropic agents dobutamine and dopamine usually increase myocardial oxygen requirements as well as coronary artery blood flow. Because the increase in blood flow is usually proportional to the increase in myocardial oxygen demand, evidence of myocardial ischemia during inotropic stimulation with dobutamine is relatively uncommon. When tachycardia develops, concurrently compromising left ventricular diastolic perfusion time and increasing myocardial oxygen requirements, abnormal myocardial metabolic function may result. Generally, the more potent β_1-receptor agonists such as dobutamine and dopamine increase myocardial oxygen consumption, whereas the less potent inotropes such as levodopa, xamoterol, and ibopamine may not.

Phosphodiesterase inhibitors appear to induce primary coronary artery vasodilatation as coronary sinus venous oxygen content increases, and myocardial oxygen extraction tends to decrease. Coronary artery blood flow either remains unchanged or increases. The observation that myocardial oxygen consumption frequently does not increase suggests that the coronary artery blood flow continues to exceed metabolic demand.

Clinical Use of Inotropic Agents

Although a large number of adrenergic and nonadrenergic agents are undergoing clinical trials, it is unlikely that any of these agents will be suitable for widespread use, particularly for the management of chronic congestive heart failure. Parenteral inotropic drugs, such as dobutamine and dopamine, and phosphodiesterase inhibitors, such as amrinone, milrinone, and enoximone, will continue to have indications for the short-term treatment of heart failure, as outlined in Table 3. Prolonged parenteral inotropic drug therapy, however, may be associated with worsening heart failure resulting from continued inotropic stimulation. Although intermittent dobutamine or amrinone infusion can provide clinical benefit in some patients with severe chronic heart failure,[41] intermittent parenteral inotropic therapy is indicated only for patients refractory to therapy with vasodilators or angiotensin-converting enzyme inhibitors or for those awaiting cardiac transplantation.

Many nonglycosidic, nonparenteral inotropic agents have undergone numerous clinical trials, but none of these agents have proved to be effective, particularly for producing sustained clinical benefit or improving the prognosis. For example, levodopa therapy produced sustained clinical benefit in some patients with chronic heart failure,[29] but long-term levodopa treatment presents many clinical problems, including drug intolerance and undesirable side effects.

Ibopamine has produced clinical benefit during short-term therapy only.[42] A few preliminary placebo-controlled studies have reported increased exercise tolerance with phosphodiesterase inhibitors such as enoximone and milrinone,[43,44] but these studies had only short-term follow-up and did not show longer survival. Indeed, a trend to higher mortality was observed in patients treated with milrinone.[44] Of all nonparenteral inotropic drugs used for the long-term management of chronic heart failure, digoxin still appears to be the most effective.[44] Thus, the use of new nonparenteral inotropic drugs, when they become available, should be limited to the treatment of specific subsets of patients with congestive heart failure (Table 3).

Summary and Conclusions

Additional controlled studies are required to assess the relative advantages of newer inotropic agents over direct vasodilators or angiotensin-converting enzyme inhibitors, both of which have been shown to decrease mortality substantially. At present, the use of the newer nonglycosidic inotropic drugs should be restricted to specific subsets of patients (Table 3).

Ventricular Arrhythmias

GARY S. FRANCIS, MD*: During the 1970s and well into the 1980s, many short-term studies of vasodilators and positive inotropic agents were conducted in patients with congestive heart failure. Although the principal objective of these studies was to establish the hemodynamic benefits of these agents, a consistent but unreported observation was the high density of complex ventricular arrhythmias, including couplets, multiformed premature ventricular contractions, and nonsustained ventricular tachycardia present in patients with advanced congestive heart failure. Moreover, as the systematic follow-up of patients with heart failure became part of large, multicenter trials, it became apparent that a sizable proportion of patients—about 30% to 40%—die suddenly and unexpectedly, presumably of ventricular arrhythmias.[3] Nearly all patients with symptomatic heart failure have complex ventricular arrhythmias, and 30% to 50% have episodes of nonsustained ventricular tachycardia by Holter monitor.[3] Among the estimated 2 million Americans with congestive heart failure, those with ventricular arrhythmias represent the single largest group at risk for sudden death.

Pathophysiology

The mechanisms of ventricular arrhythmias in patients with congestive heart failure include reentry, abnormal automaticity, and related phenomena after depolarizations and triggered activity. Congestive heart failure is characterized by potentiating conditions that may facilitate arrhythmias. These possible conditions include a combination of myocardial ischemia, mechanical factors, electrolyte imbalance, increased circulating catecholamines, and high basal sympathetic activity, inotropic therapy, or antiarrhythmic therapy.

Myocardial Ischemia

Because a large proportion of patients with congestive heart failure has underlying coronary artery disease, acute

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myocardial ischemia, silent or clinically overt, may be arrhythmogenic in many patients. This concept has important therapeutic implications—it suggests that therapies like nitrates, β-blockers, and coronary artery bypass should be considered for many patients. There is no practical, widely available method to identify heart failure patients at risk of suffering myocardial ischemia and subsequent arrhythmias, however. Ventricular arrhythmias on Holter monitoring in patients with congestive heart failure have not predicted sudden death. Moreover, the potential of anti-ischemic therapy to produce antiarrhythmic effects in patients with heart failure and severe coronary artery disease is unclear. There is little evidence that acute ischemic episodes precipitate life-threatening ventricular arrhythmias in patients with well-established coronary artery disease and heart failure. Most coronary revascularization studies fail to show any lessening of ambient ventricular arrhythmias. It is most likely that the myocardial scar rather than acute ischemia per se is the substrate for most sustained, life-threatening arrhythmias, but without a valid, readily applied method to detect acute ischemic episodes in patients with heart failure, the importance of this potentiating condition remains unknown.

Mechanical Factors

Local mechanical factors in the left ventricle may play a role in the pathogenesis of arrhythmias in heart failure, especially in patients with segmental wall motion abnormalities. The morphology of the electrical signal of the heart can vary according to mechanoelectric feedback. The abnormal mechanics of contraction may initiate an arrhythmia through a close interaction between membrane and mechanical events at the cellular level.[45] For example, mechanically induced electrical changes may modify intracellular calcium, which could affect membrane sodium-calcium exchange[46] and thereby prolong the duration of the action potential. Such mechanical influences occurring late in the cardiac cycle could also change intracellular calcium levels to produce early afterdepolarizations. Given the reduced efficacy of the use of conventional antiarrhythmic drugs in patients with congestive heart failure, mechanoelectric disturbances may be important in generating arrhythmia in this patient population. For patients with symptomatic life-threatening arrhythmias and ventricular aneurysms, the only rational therapy short of heart transplant involves myocardial mapping before and during aneurysmectomy, sometimes combined with a bypass operation, antiarrhythmic drugs, and automatic implantable cardioverter-defibrillators.

Electrolyte Imbalance

The prevalence of electrolyte disturbances in patients with congestive heart failure is well known—hypokalemia and hypomagnesemia are both associated with complex ventricular arrhythmias. A vigorous use of diuretics and high levels of circulating aldosterone also contribute to these disturbances. Studies by Dargie and colleagues indicate an important inverse relationship between serum potassium levels and ventricular arrhythmias in these patients.[47] The influence of supplemental potassium on ventricular arrhythmias has not been systematically studied in patients with congestive heart failure, but a reasonable approach would be to maintain serum potassium levels in the high to normal range, 4 to 5 mmol per liter. The angiotensin-converting enzyme inhibitors captopril and enalapril, which maintain or increase serum potassium levels by inhibiting the renin-angiotensin-aldosterone system, have reduced ventricular arrhythmia density in some patients with congestive heart failure.[48,49]

Sympathetic Activity

Sympathetic nervous system activity, measured directly by neurographic techniques or indirectly by plasma norepinephrine levels,[50] is increased in patients with congestive heart failure.[51] There is a clear association between circulating plasma norepinephrine levels and mortality[52] and a significant relation between premature ventricular contraction density and plasma norepinephrine levels[47] in patients with congestive heart failure. β-Adrenergic blockers have improved function in selected patients with dilated cardiomyopathy, and administering angiotensin-converting enzyme inhibitors has produced short-term reductions in plasma norepinephrine levels and ventricular arrhythmias, along with improved survival, in patients with class IV congestive heart failure.[5] Together these data suggest that excessive sympathetic drive may contribute to the poor survival rate of patients with congestive heart failure and that treatment to reduce sympathetic activity may be beneficial, perhaps in part through an antiarrhythmic effect.

Inotropic Therapy

Under certain conditions, inotropic therapy, including digitalis, has a well-known proarrhythmic effect. All positive inotropic agents have the potential to enhance arrhythmias by inducing acute myocardial ischemia and by direct effects on transmembrane potential. Large doses of dopamine[53] and dobutamine[54] are clearly arrhythmogenic, and digitalis was retrospectively implicated in the lower survival of patients who had sustained a myocardial infarction.[55] There are, however, no prospective data on the influence of digitalis on survival,[56] and digitalis remains a widely used agent to treat congestive heart failure. The National Institutes of Health and the Department of Veterans Affairs are planning a multicenter, prospective, placebo-controlled trial to study the influence of digitalis on survival in patients with congestive heart failure. Until more data are available from this and similar trials, all positive inotropic agents, including digitalis, should be considered potentially arrhythmogenic in these patients.

Antiarrhythmic Therapy

Another possible cause of life-threatening arrhythmias in patients with congestive heart failure may be antiarrhythmic therapy itself. In the Vasodilator-Heart Failure Trial, the use of antiarrhythmic therapy was a significant risk factor for shortened survival in patients with heart failure.[57] Because there was no intent to control for antiarrhythmic therapy in this trial, we cannot know if the increased mortality resulted from antiarrhythmic therapy or from inherent selection bias.

Antiarrhythmic therapy is generally thought to carry a 10% to 15% risk of proarrhythmia, depending on how that term is defined.[58] In patients with advanced congestive heart failure, proarrhythmic risk may be even higher. Side-effect profiles for antiarrhythmic drugs may also be more prominent in these patients, a finding that may relate to greatly altered pharmacokinetics and pharmacodynamics.[59] In addition, patients with severe left ventricular dysfunction (ejection fraction of $<35\%$) seem less responsive to antiarrhythmic agents.[60] One small uncontrolled trial showed no

difference in survival when 43 patients with severe heart failure were followed during two years of treatment with a type IA antiarrhythmic drug versus no antiarrhythmic therapy.[9] Thus, left ventricular dysfunction rather than the pharmacologic control of ventricular arrhythmias may be the driving force behind the high mortality rate in patients with heart failure.[61] Because of the risks of drug-aggravated arrhythmias, heightened side effects, enhanced myocardial depression, and general ineffectiveness, the empiric use of type I antiarrhythmic drugs in patients with asymptomatic ventricular arrhythmias and heart failure is not recommended.

Management

The consensus is that patients with heart failure and symptomatic ventricular tachyarrhythmias should be treated following incidents such as a cardiac arrest or an episode of sustained ventricular tachycardia with lightheadedness. Some consider electrophysiologic testing to be of value in patients with symptomatic arrhythmias,[62] particularly in those with ischemic heart disease. A combination of exercise testing, Holter monitoring, and electrophysiologic testing has been used to determine the effectiveness of combination therapy, including giving amiodarone and β-blockers.[63] Signal-averaged electrocardiograms may also be useful in identifying patients at risk for sudden death. No uniformly accepted protocol exists, however, to assess antiarrhythmic drug efficacy in treating symptomatic ventricular arrhythmias in patients with heart failure. Nevertheless, the best approach is to undertake treatment while patients are in hospital and monitored by continuous electrocardiography.[64] Comprehensive treatment should always include maintaining an optimal electrolyte balance and hemodynamic status. In contrast to the general agreement about the treatment of symptomatic ventricular tachyarrhythmias, substantial controversy continues about the treatment of asymptomatic ventricular tachyarrhythmias in patients with heart failure.[65] Electrophysiologic testing in these patients, especially in those with primary dilated cardiomyopathy, is of limited value.[66]

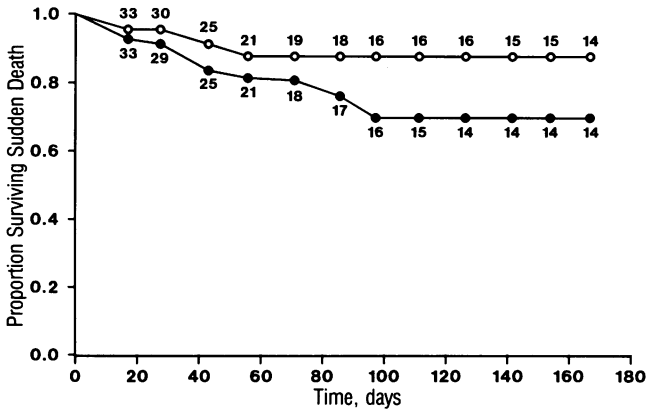

Figure 1.—Cumulative rates of survival without sudden death were compared for patients who received no antiarrhythmic therapy **(closed circles)** and patients who received quinidine, procainamide, or amiodarone **(open circles).** The numbers represent study participants available for follow-up (from Simonton et al[67]).

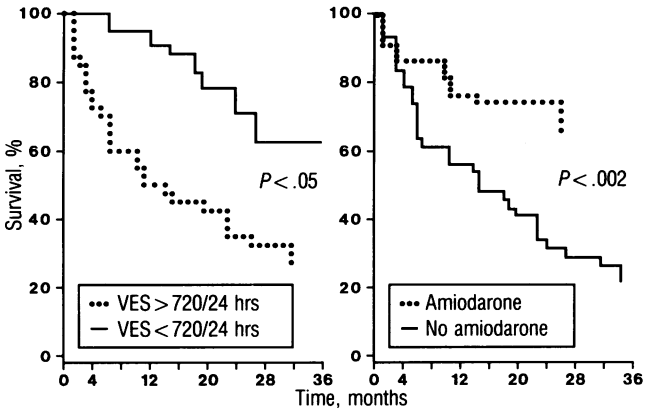

Figure 2.—A Kaplan-Meier analysis shows the influence of ventricular extrasystoles (VES) and the administration of amiodarone on the survival of 84 patients with chronic heart failure (from Cleland et al[48]).

Several small, uncontrolled trials have evaluated empiric antiarrhythmic drug therapy in patients with congestive heart failure. An uncontrolled study by Simonton and co-workers found that antiarrhythmic therapy decreased the frequency of sudden death in 82 patients treated with phosphodiesterase inhibitors (Figure 1).[67] Of these patients, 43 received no antiarrhythmic therapy, and the others received quinidine, procainamide, or amiodarone. At six months, sudden death had occurred in 29% of patients not receiving antiarrhythmic therapy and in only 13% of patients receiving antiarrhythmic drugs. Similar results were reported by Neri and associates, who noted dramatically reduced premature ventricular contractions in more than 70% of patients with congestive heart failure treated with amiodarone for three years.[68] In a prospective crossover study, Cleland and colleagues also found that small doses of amiodarone (mean dose, 183 mg per day) greatly reduced the frequency of life-threatening ventricular arrhythmias and the overall mortality rate among patients with severe heart failure (Figure 2). A recently reported randomized, placebo-controlled trial of amiodarone in patients with severe heart failure failed to show any benefit to drug-treated patients.[69]

Although some of these studies were not randomized (and thus were subject to selection bias)[48,67,68] and may have been too small to measure statistically significant effects on mortality,[69] they are important because they suggest that amiodarone can suppress ventricular arrhythmias,[48,67,68] and its use may be reasonably well tolerated[69] by patients with advanced congestive heart failure. Moreover, they bring into focus a testable hypothesis: Antiarrhythmic drug therapy may improve survival in patients with congestive heart failure. Data are as yet insufficient to recommend antiarrhythmic drug therapy to prolong the survival of patients with asymptomatic ventricular arrhythmia.

Summary and Conclusions

Life-threatening ventricular arrhythmias are common in patients with congestive heart failure, and about 30% to 40% of these patients die suddenly. Many mechanisms are probably involved in the pathogenesis of these arrhythmias; therefore, no single therapy is likely to be effective. Symptomatic ventricular arrhythmias should be treated; such therapy might include more than one antiarrhythmic agent, surgical therapy, and automatic implantable cardioverter-defibrillators. The role of antiarrhythmic drug therapy for asymptomatic ventricular arrhythmias in patients with heart failure remains uncertain, but preliminary studies suggest that amiodarone may be useful. The Department of Veterans Affairs has recently begun a randomized, placebo-controlled trial to test the hypothesis that the use of amiodarone may

prolong survival in patients with chronic congestive heart failure.

Ventricular Remodeling After Myocardial Infarction

BRIAN G. FIRTH, MD, DPhil*: Coronary atherosclerosis with resultant myocardial infarction is the most important single cause of heart failure in the United States today. After a first acute myocardial infarction, overt heart failure develops in only a minority of patients, but 14% of these patients will have heart failure within five years and 22% within ten years.[70] Late heart failure may result from further myocardial infarction, with a further loss of functional myocardium, or from dilatation and remodeling of the heart.

The amount of irreversibly damaged myocardium after one or more infarctions is the single greatest determinant of long-term survival.[71] Although the left ventricular ejection fraction has been widely used as a postinfarction index of residual myocardial function, Hammermeister and associates suggested ten years ago that the left ventricular volume may be a more sensitive predictor of outcome than the ejection fraction.[72] Recent work by White and colleagues supported this notion with the demonstration that, although the left ventricular ejection fraction is an important predictor of postinfarction survival, patients with larger end-systolic volumes at any given ejection fraction have a worse prognosis over eight years than those with smaller volumes.[73] Thus, the degree of left ventricular dilatation and remodeling following myocardial infarction appears to be of cardinal importance.

Pathophysiology of Dilatation

Klein, Herman, and Gorlin determined that the stroke volume could not be maintained without ventricular dilatation if more than 20% of the ventricular wall is destroyed.[74] Kitamura and co-workers also drew attention to "the geometric and functional abnormalities of the left ventricle" that occur "with a chronic localized noncontractile area."[75] Investigators at Johns Hopkins Medical School (Baltimore, Md) later attempted to define more precisely the consequences of localized myocardial damage by doing a series of important studies in humans and in a rat model of myocardial infarction.

Hutchins and Bulkley performed autopsies on 76 consecutive patients who died within 30 days after an acute myocardial infarction.[76] Infarct extension—histologically more recent foci of contraction-band necrosis around an infarct—was noted in 13 autopsies (17%). Infarct expansion, however—acute dilatation and thinning of the infarct area not explained by additional myocardial necrosis—was seen in 45 autopsies (59%). Severe infarct expansion did not develop until five days after infarction and was greater with first and transmural anterior infarcts.

In a subsequent study, Eaton and associates performed serial two-dimensional echocardiographic studies of 28 patients within 14 days of acute infarction.[77] They observed a progressive increase in infarct-segment length in 8 patients, whom they designated as "expanders," but essentially no change in infarct-segment length in the other 20. Again, infarct expansion occurred predominantly in those with large anterior or anteroseptal transmural infarcts. Expansion was detected by 3 days after infarction and appeared to continue for at least the first 14 days. In this study, the authors suggested that dilatation and expansion involved only the infarct region. A subsequent study by this group found lengthening of both the infarcted and uninfarcted segments extended for 3 to 30 months after infarction in 13 patients with transmural anterior myocardial infarction.[78] Of the 13 patients, 7 showed evidence of infarct expansion by two-dimensional echocardiography, and the segmental dilatation rate averaged 1 mm per month for both infarcted anterior wall and uninfarcted posterior wall segments. Thus, left ventricular dilatation seems to involve a stretching of both the infarcted and uninfarcted myocardial segments.

The Johns Hopkins investigators did further studies of postinfarction myocardial remodeling in rats.[79] Transmural infarcts were produced in 45 rats by ligating the left coronary artery; rats were killed on days 1, 2, and 3 after infarction. (In rats, ligating the left coronary artery does not produce septal infarction, and histopathologic changes, myocardial thinning, dilatation, and remodeling occur about twice as rapidly as in humans.) Of the 45 rats, infarct expansion developed in 28. The 17 without infarct expansion had a mean infarct size of 22% $\pm$ 2% of left ventricular mass, which was significantly smaller than that of the 28 with infarct expansion: Mean infarct size as a percentage of left ventricular mass was 35% $\pm$ 4% for those with 1+, 42% $\pm$ 5% for those with 2+, and 45% $\pm$ 5% for those with 3+ to 4+ expansion. Thus, infarct size does appear to have a bearing on infarct expansion, but, beyond a certain size, other factors may determine the severity of expansion. In rats showing evidence of expansion, wall thickness decreased 55% in the infarct zone and 28% in the remote uninfarcted region. This confirmed that the uninfarcted myocardium is intimately involved in the postinfarction dilatation process.

Factors That May Affect Dilatation

Because the infarct size does not appear to be the sole determinant of the severity of infarct expansion after myocardial infarction, Nolan and colleagues investigated the effect of increased afterload on this process.[80] In that study, 40 rats were randomly assigned to aortic banding (n = 20) or a sham operation (n = 20) and allowed to recover for three weeks. They were then randomly assigned to left coronary artery ligation (n = 30) or a sham operation (n = 10). Rats were killed seven days later, and morphologic changes in the myocardium were characterized. Although infarct size as a percentage of left ventricular mass was smaller at death in rats with aortic banding, infarct expansion as measured by cavity dilatation and infarct thinning occurred in both groups but was greater in rats with aortic banding.

The extent to which increased afterload per se, as opposed to a resultant myocardial hypertrophy, was responsible for these effects is uncertain. It is also uncertain how the observed effects of a short-term increase in afterload relate to those of chronic systemic arterial hypertension, their clinical counterpart. Nevertheless, the rat study results seem to be consistent with the observation that myocardial rupture as a sequela of infarct thinning and expansion is more common in patients with systemic arterial hypertension.[81] This study also included the important observation that hypertrophy of uninfarcted myocardium occurred in response to myocardial infarction.[80] Recent evidence suggests that such hypertrophy may be pathologic because it may be associated with a change

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in myosin isoform from V_1 to V_3 and with a localized, depressed coronary artery vasodilator reserve.[82]

Various other factors may contribute to left ventricular dysfunction after infarction. These include variable collagen ingrowth into the infarcted region, subendocardial ischemia, cellular calcium overload, catecholamine toxicity, decreased β-receptor regulation, a reduced amount of myocardial stimulatory guanine nucleotide regulatory protein, dyssynchronous contraction, and interaction between right and left ventricles. In addition, the use of certain drugs, including corticosteroids and nonsteroidal anti-inflammatory agents, may aggravate this process.[83]

Left Ventricular Dilatation in Humans

Recent studies in humans not only confirm many of the observations in rats but also consider the possible role of infarct-related artery patency in preventing or ameliorating left ventricular dilatation. McKay and co-workers did coronary angiography and left ventriculography within the first few hours of infarction and again at 14 days in 30 patients who received thrombolytic therapy.[84] The only patients included in their report were those who showed early improved flow in the infarct-related artery. Despite this, left ventricular end-systolic and end-diastolic volume indices increased significantly ($P < .01$) in the group as a whole at two weeks. The increase in the left ventricular end-diastolic volume index correlated directly ($r = .71$, $P < .001$) with infarct size, measured as the percentage of the ventriculographic silhouette that was akinetic or dyskinetic at the initial catheterization. The mean endocardial-perimeter length increased 13% in infarcted segments and 19% in uninfarcted segments. At the same time, decreased left ventricular filling pressures and increased cardiac output occurred at the expense of a substantial increase in ventricular chamber volumes.

These investigators also studied the time course of left ventricular dilatation in 36 patients, with serial radionuclide ventriculograms taken at 1 and 11 days and at 10½ months after acute transmural myocardial infarction.[85] In 20 of the 36 patients, the left ventricular volume increased more than 20%. Left ventricular dilatation was more frequent and chronic dilatation significantly more pronounced ($P < .01$) in patients with left anterior descending as opposed to right coronary artery occlusion (Figure 3). These investigators could not discern a difference in left ventricular volumes or ejection fraction among patients with successful versus unsuccessful thrombolysis at four to six hours.

Jeremy and associates also evaluated the effect of infarct artery patency on subsequent changes in ventricular volume and came to a diametrically opposite conclusion.[86] In their study of 40 patients who did not receive thrombolytic therapy, infarct artery perfusion was documented by predischarge coronary angiography, and left ventricular volumes were measured at 48 hours and 1 month after a first acute myocardial infarction. By multiple linear regression analysis, the degree of perfusion of the infarct artery ($r = .58$, $P = .001$) was a more important predictor of volume change than was infarct size measured by peak creatine kinase levels ($r = .30$, $P = .009$). Left ventricular dilatation—an increase of 20% or more in volume—occurred in all 14 patients who did not have perfusion of the infarct-related artery but in only 2 of the 26 patients who had perfusion of this artery due to subtotal occlusion or collateral vessels. The importance of perfusion of the infarct-related artery and the time at which it should occur to limit left ventricular dilatation remain matters of considerable debate.

Effects on Dilatation of Therapy With Angiotensin-Converting Enzyme Inhibitors

Although many factors may affect ventricular dilatation and remodeling, it seems likely that increased wall stress is among the most important. Pfeffer and colleagues tested this hypothesis in a rat model of myocardial infarction.[87] At 2 or 21 days following left coronary artery ligation, 104 rats were randomly assigned to treatment with standard drinking water or with the angiotensin-converting enzyme inhibitor captopril in standard drinking water. After three months of this regimen, hemodynamic measurements were made before and during volume loading experiments, and then the animals were killed. Although infarct size as a percentage of left ventricular mass did not differ between the groups, left ventricular end-diastolic pressure was significantly lower ($P < .01$) in captopril-treated rats with small, moderate, or large infarcts. In response to volume loading, captopril-treated rats had higher peak stroke volumes and lower left ventricular volumes than control animals. Finally, captopril treatment improved relationships between diastolic pressure and volume, allowing infarcted hearts to function at smaller volumes and lower left ventricular filling pressures.

The same laboratory conducted a later placebo-controlled study of 302 rats with myocardial infarction to determine effects on one-year survival of administering captopril beginning on day 14 after an infarction.[88] As expected, survival was directly related to infarct size in placebo-treated rats. Overall survival was significantly greater ($P < .02$) in the captopril-treated group, however, with the most pronounced benefit occurring in rats with moderate-sized infarcts. This improved survival also appeared to be related to the attenuation of ventricular dilatation.

Finally, this group did a pilot study in 59 patients to assess the efficacy of prophylactic treatment with an angiotensin-converting enzyme inhibitor after a first anterior transmural myocardial infarction.[89] Patients, all of whom had left ventricular ejection fractions of 45% or lower and no overt heart failure, underwent cardiac catheterization approximately 18 days after infarction and were randomly assigned to captopril or placebo treatment for a year. Captopril was discontinued 20 hours before catheterization at one year. At this time, significant decreases from baseline values were observed in left ventricular end-diastolic pressure ($P < .005$), pulmo-

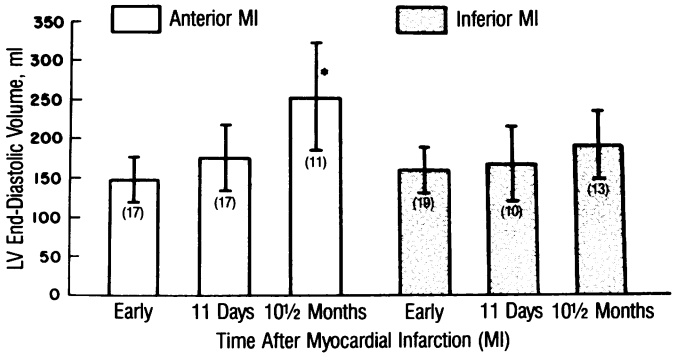

Figure 3.—Left ventricular (LV) end-diastolic volume after myocardial infarction was measured in patients with anterior versus inferior infarction. Asterisk indicates $P < .01$ for anterior MI versus inferior MI at 10½ months. Numbers in parentheses are the number of patients (from Warren et al[85]).

nary capillary wedge pressure ($P < .01$), and mean pulmonary artery pressure ($P = .05$) in captopril-treated but not in placebo-treated patients. Conversely, left ventricular end-diastolic volume increased significantly ($P < .02$) in placebo-treated but not in captopril-treated patients. Intergroup analyses for these variables did not achieve statistical significance, however.

These preliminary results showed that the two most important predictors of ventricular dilatation were persistent occlusion of the infarct-related artery at baseline catheterization and the extent of wall-motion abnormality, defined as akinesis plus dyskinesis of 30% or more of the diastolic perimeter at baseline. The greatest benefit of treatment with the angiotensin-converting enzyme inhibitor was seen in those with a closed infarct-related artery and akinesis plus dyskinesis of more than 30% (Figure 4). Another recent study by Sharpe and colleagues evaluated 60 patients after acute myocardial infarction.[90] Their observations also supported the conclusion that treatment with angiotensin-converting enzyme inhibitor may have a beneficial effect on left ventricular dilatation and remodeling.

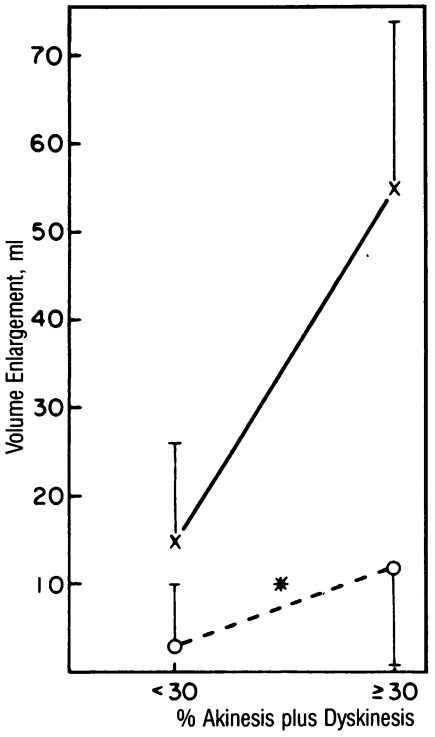

Figure 4.—An increase in left ventricular end-diastolic volume (volume enlargement) is shown in patients with occlusion of the left anterior descending coronary artery at baseline catheterization (n = 36). The dotted line represents the values for patients receiving captopril, the solid line those receiving placebo. The asterisk denotes significance at $P < .05$ (from Pfeffer et al[89]).

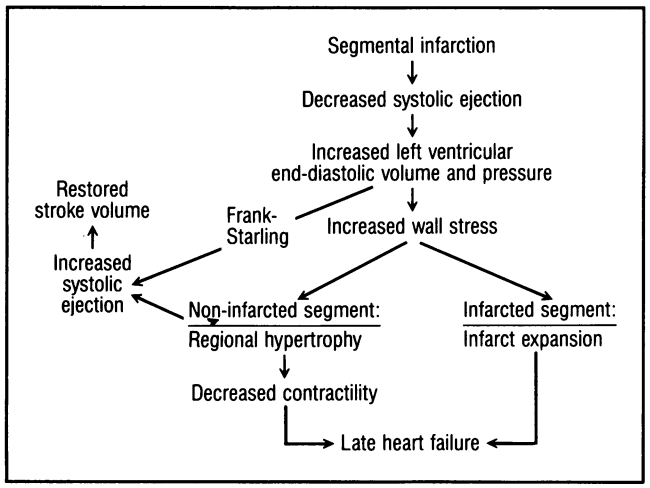

Figure 5.—The schematic represents the hypothesis proposed to account for mechanisms of left ventricular remodeling (from McCay et al[84]).

Summary and Conclusions

Although studies in animals and humans suggest that treatment with angiotensin-converting enzyme inhibitors may be beneficial, such data should be regarded as preliminary until results of the much larger Survival and Ventricular Enlargement (SAVE) and Studies of Left Ventricular Dysfunction (SOLVD) trials become available. McKay and associates have presented a useful hypothesis to explain the sequence of events that causes segmental left ventricular dysfunction to result in increased wall stress and ultimately in left ventricular dilatation, remodeling, and overt heart failure (Figure 5).[84] Conceivably, angiotensin-converting enzyme inhibitors may attenuate left ventricular dilatation by unique properties such as abolishing the toxic effects of angiotensin II on myocardium or mitigating the effects of reduced myocardial stimulatory guanine nucleotide regulatory protein. It seems more likely, however, that effects of these drugs on dilatation relate to reducing systolic and diastolic wall stress without an accompanying reflex increase in catecholamines during the remodeling period.

It is worth recalling that β-blockers appear to reduce all causes of postinfarction mortality, including myocardial rupture and progression to congestive heart failure.[91] Thus, overlapping benefits may accrue from a combined use of angiotensin-converting enzyme inhibitors and β-blockers. Even earlier intervention with such agents, aimed at limiting infarct size and reducing wall tension as soon as possible after infarction, may have an even more salutary effect on left ventricular dilatation than when postinfarction treatment begins within days to weeks.[92] Further studies will be needed to answer these questions definitively and to determine possible incremental benefits of such therapy in conjunction with thrombolytic therapy or emergency angioplasty for acute myocardial infarction.

One conclusion seems clear: To make a serious impact on the escalating mortality from congestive heart failure, we will need to intervene much earlier. This implies not only preventing left ventricular dilatation and remodeling but also limiting myocardial infarct size and attempting to reduce the incidence of infarction by dealing more effectively with well-recognized risk factors such as cigarette smoking, hyperlipidemia, and hypertension.

Adjuvant Therapy for Coronary Reperfusion—Role of Oxygen-Radical Scavengers?

ROBERT A. KLONER, MD, PhD, in collaboration with KARIN PRZYKLENK, MD*: In the past, the fate of ischemic myocardium was thought to be determined primarily by the imbalance between oxygen supply and demand. Interventions aimed at reducing myocardial ischemic injury either enhanced oxygen supply (usually by increasing coronary blood flow or coronary collateral flow) or reduced oxygen demand (usually by decreasing the heart rate, afterload, or contractility). Recent evidence suggests, however, that myocardial in-

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jury may be exacerbated by cytotoxic, oxygen-derived free radicals generated during ischemia or reperfusion. This oxygen-radical theory of ischemic and reperfusion injury raised the potential for new therapies to attempt to blunt myocardial damage by scavenging these reactive oxygen species. In this section we will discuss coronary artery reperfusion as a complex phenomenon with both beneficial and potentially deleterious consequences; the oxygen-radical theory of tissue injury; pharmacologic adjuvant therapy for acute myocardial infarction and stunned myocardium; and the possible role of agents such as calcium-channel blockers, β-blockers, and oxygen-radical scavengers.

Coronary Artery Reperfusion Phenomena

Beneficial Effects of Early and Late Reperfusion

Coronary artery perfusion after acute myocardial infarction unquestionably has beneficial effects[93]: Timely reperfusion has been shown to limit myocardial infarct size,[94] to improve left ventricular function,[95] and to enhance survival.[96] Although early reperfusion—within three to four hours of the start of ischemia—is most likely to salvage ischemic myocardium, our laboratory and others have also observed benefits of late coronary artery reperfusion in experiments in animals.

Delayed reperfusion did not reduce infarct size or salvage previously ischemic myocardium, but it did produce a thicker infarct scar and reduce myocardial infarct expansion.[97] In addition, late coronary reperfusion appeared to have beneficial effects on ventricular arrhythmias, as assessed by ambulatory electrocardiographic monitoring four days after coronary artery occlusion.[98] Reperfusion six hours after occlusion reduced the total runs of ventricular tachycardia as well as the frequency of runs of greater than 200 beats per minute and of runs longer than 60 seconds. Finally, late reperfusion resulted in a patent, infarct-related coronary artery, which may serve as both a source of coronary collateral blood flow to other jeopardized areas of the heart and a route by which pharmacologic agents such as antiarrhythmics can penetrate peri-infarct tissue. The beneficial effects of delayed reperfusion may in part explain the reduced mortality observed in patients receiving thrombolytic therapy as late as 13 to 24 hours after symptoms began in the Second International Study of Infarct Survival (ISIS-2) trial[99] and the reduced mortality without reduced infarct size observed in the western Washington trial.[100]

Potentially Deleterious Effects of Reperfusion

The potentially deleterious consequences of reperfusion have been reviewed in detail previously[93] and include explosive cell swelling, hemorrhagic myocardial infarction, the no-reflow phenomenon, "stunned myocardium," "reperfusion injury," and ventricular arrhythmias. Cytotoxic oxygen radicals, formed during ischemia and reperfusion, are thought to play an important role in some of these deleterious effects, including stunned myocardium, reperfusion injury, no-reflow, and reperfusion arrhythmias.[101]

Oxygen-Radical Theory of Tissue Injury

A free radical is a molecule with an odd, unpaired electron. This unpaired electron makes the molecule unstable and highly reactive. Reactive oxygen species thought to be generated during ischemia and reperfusion—the superoxide anion, the hydroxyl radical, and their intermediary hydrogen peroxide—can result in lipid peroxidation of membranes and denaturation of proteins. Such damage can impair cell-membrane permeability, lead to altered function of myocardial cellular organelles including sarcoplasmic reticulum, and possibly result in cell death.[102] Exposure of the myocardium to oxygen radicals can result in myocyte injury[103] and depressed cardiac function.[104]

Evidence from these in vitro and in vivo experiments suggests that oxygen-centered radicals may be generated during ischemia and reperfusion. Oxygen radicals have been detected in the myocardium and coronary effluent of hearts subjected to transient ischemia.[105] Other investigators have documented depletion of the normal, endogenous enzymatic defenses against free-radical injury following transient ischemic episodes, suggesting that oxygen free radicals may have been present in the myocardium during ischemia and reperfusion. Potential sources for the generation of oxygen radicals during ischemia and reperfusion include the xanthine oxidase reaction,[106] although this reaction is species dependent[107]; activated neutrophils[108,109]; mitochondria[110]; and arachidonic acid metabolism.

Adjuvant Therapy for Acute Myocardial Infarction—A Potential Role for Oxygen-derived Free-Radical Scavengers?

Adjuvant therapy for acute myocardial infarction refers to the administration of pharmacologic agents along with thrombolytic therapy or angioplasty to further improve outcome. Acute adjuvant pharmacologic therapy could improve the function of the heart by enhancing the recovery of stunned myocardium (postischemic dysfunction of viable, reperfused myocytes); increase the "window in time" in which reperfusion effectively reduces myocardial infarct size so the adjuvant agent plus reperfusion would reduce infarct size more than reperfusion alone; maintain vessel patency following thrombolysis, thereby reducing the incidence of reocclusion; and reduce or prevent reperfusion arrhythmias. We will discuss adjuvant therapy for stunned myocardium and reperfused infarction as well as the possible role of adjuvant agents, such as calcium blockers, β-blockers, and oxygen-radical scavengers, administered during the acute phase of ischemia and reperfusion.

Adjuvant Therapy for Stunned Myocardium

The term "stunned myocardium" refers to viable myocardium, salvaged by reperfusion, in which there is prolonged but reversible postischemic contractile dysfunction.[111] This phenomenon was first described following 15 minutes of coronary artery occlusion in dogs. This ischemic period did not cause myocyte death but did cause abnormal regional contractile function in salvaged tissue, an effect that persisted for hours to days after reperfusion.[111] This myocardial dysfunction occurred after prolonged transient coronary artery occlusion—a subendocardial infarct was produced in two hours. In this instance, however, subepicardial tissue salvaged by reperfusion remained stunned for days to weeks after reflow.[111]

Considerable experimental evidence suggests that oxygen-derived free radicals play a role in the pathogenesis of stunned myocardium. This hypothesis is supported by several studies in which potent free radical-scavenging enzymes, superoxide dismutase plus catalase, were administered preceding 15 minutes of coronary artery occlusion in

anesthetized open-chest dogs. Pretreatment with the scavenging agents consistently enhanced regional contractile function of stunned, postischemic tissue during the initial two to three hours after reflow compared with that of controls pretreated with a saline solution.[112] Similar beneficial results were more recently obtained with other free-radical scavengers, as reviewed by Bolli.[113] Antioxidants, iron chelators, quenching agents, and spin traps[105,113] have all been shown to improve contractile function of postischemic, stunned myocardium in the canine model.

There is little doubt that oxygen free radicals contribute to the phenomenon of stunned myocardium, but sources of these free radicals—the xanthine oxidase reaction,[106,107] activated neutrophils,[108,109] the mitochondrial electron transport chain,[110] or arachidonic acid metabolism—in these models of brief, transient ischemia remain speculative. For example, Engler and Covell reported that the virtual elimination of neutrophils by leukocyte filtration ablated postischemic contractile dysfunction produced by 15 minutes of coronary artery occlusion in anesthetized dogs.[114] In contrast, other investigators failed to document any beneficial effect of neutrophil filtration[115] or suppression[116] on the recovery of regional contractile function in dogs. Furthermore, both our laboratory[117] and others[118] have found that transient coronary artery occlusion does not appear to be associated with neutrophil infiltration. Thus, the importance of neutrophils in the pathogenesis of stunned myocardium in models of brief ischemia is questionable. Two- to three-hour periods of ischemia causing myocardial cell death have been associated with neutrophil influx following reperfusion, however[108]; thus, neutrophils could contribute pathogenically to the phenomenon of stunned myocardium in the peri-infarct zones.

It should be noted that all agents that scavenged, quenched, or otherwise inhibited free-radical production restored the contractile function of stunned myocardium to a maximum of only 50% to 70% of baseline preocclusion values.[112] These data suggest that other mechanisms—including abnormalities in calcium metabolism, abnormal energy transduction, and the low-reflow phenomenon—may also be important causes or mechanisms of postischemic contractile dysfunction. Several recent studies suggest that alterations of calcium flux may contribute to the phenomenon of stunned myocardium. Intravenous nifedipine administered 30 minutes after reperfusion[119] in anesthetized dogs virtually ablated stunned myocardium. The parenteral administration of nifedipine may have enhanced the return of function of stunned myocardium by reducing afterload or increasing postreperfusion myocardial blood flow. A minute intracoronary dose of nifedipine, however, which did not alter hemodynamics or regional myocardial blood flow, also restored the function of stunned myocardium, suggesting that the drug had a direct effect on myocardial cells.[119] The treatment of stunned myocardium with verapamil—before occlusion, at reflow, or 30 minutes after reperfusion—also enhanced the return of function.[120]

Could there be a connection between the beneficial effects of oxygen-derived free-radical scavengers and calcium blockers? Theoretically, these two seemingly diverse mechanisms may be interrelated. Oxygen free radicals generated during ischemia and reperfusion can cause lipid peroxidation of cell membranes. Damaged membranes could make myocardial cells more susceptible to alterations in calcium flux. These alterations might include not only the influx of calcium into cells but also fluxes of calcium within intracellular pools—between the sarcoplasmic reticulum and actin-myosin filaments. In addition, the conversion of xanthine dehydrogenase to xanthine oxidase (important in the ultimate generation of superoxide radicals) is thought to be mediated by calcium-dependent proteases. Thus, these hypothetical links between oxygen radicals and alterations in calcium flux may play a role in the pathogenesis of stunned myocardium.

Other adjuvant therapies have been explored in models of stunned myocardium. The use of angiotensin-converting enzyme inhibitors and afterload reducers like hydralazine have improved the function of stunned myocardium.[121]

Adjuvant Therapy to Reduce Myocardial Infarct Size

Timely coronary artery reperfusion unquestionably reduces myocardial infarct size, but whether adjuvant pharmacologic therapy can reduce infarct size more than reperfusion alone remains controversial. Various types of pharmacologic agents have been tested as adjuvants. In some studies, administering pharmacologic therapy during both ischemia and reperfusion was shown to be of benefit. In anesthetized dogs, Reimer and Jennings observed that administering verapamil preceding a 40-minute coronary artery occlusion plus reperfusion reduced infarct size more than reperfusion alone.[122] With the duration of ischemia extended to three hours, however, the beneficial effect of the calcium blocker was lost. Similarly, our laboratory reported that the intracoronary administration of verapamil did not reduce infarct size more than reperfusion alone.[123]

Some studies have suggested that β-blockers combined with reperfusion may further limit myocardial infarct size. Hammerman and co-workers showed that administering timolol during a three-hour experimental coronary artery occlusion followed by reperfusion reduced myocardial infarct size.[124] Studies in other experimental models, however, suggested that the use of propranolol did not reduce myocardial infarct size.[125] A potential mechanism of both calcium and β-blockers in these models is reducing oxygen demand during ischemia.

Certain forms of adjuvant therapy have been shown in large clinical trials to be beneficial. For example, in the ISIS-2 collaborative group trial, the combination of streptokinase with aspirin reduced the incidence of vascular deaths due to suspected acute myocardial infarction more than the use of either agent alone.[99] Aspirin therapy also reduced the incidence of nonfatal reinfarction that was observed with using streptokinase alone. In the Phase II Thrombolysis in Myocardial Infarction trial, the combination of tissue plasminogen activator plus early metoprolol therapy reduced the incidence of nonfatal reinfarction and recurrent ischemic episodes.[126] Data on the role of calcium blockers in patients receiving thrombolytic therapy are limited. In patients without thrombolysis, calcium blockers have generally not reduced infarct size or prolonged survival. Some have been shown to reduce the severity of postinfarct angina pectoris and possibly to reduce the incidence of reinfarction after non-Q-wave infarction. Table 4 lists possible forms of adjuvant pharmacologic therapy for acute myocardial infarction.

Oxygen-derived Free Radicals and Reperfusion Injury

Investigators have postulated that oxygen-derived free-radical scavengers might serve as useful adjuvant therapy for acute myocardial infarction.[127] This concept is based on the

TABLE 4.—*Initial Adjuvant Agents Used With Thrombolytic Therapy for Acute Myocardial Infarction*

Agent	*Comment*
Aspirin	In the ISIS-2 trial, aspirin therapy improved survival and reduced nonfatal reinfarction; other antiplatelet agents are being investigated
β-Blockers	In the TIMI II trial, early metoprolol administration reduced the incidence of nonfatal reinfarction and recurrent ischemia; effects of β-blockers on experimental infarct size in reperfusion models have been variable
?Heparin	After successful thrombolysis, heparin therapy may reduce the incidence of reocclusion
?Calcium blockers	In several experimental studies in reperfusion models, calcium blockers reduced myocardial infarct size; in clinical studies without reperfusion, they did not affect infarct size; clinical data on combining calcium blockers and reperfusion are limited; calcium blockers do decrease the severity of postinfarct angina and may reduce the incidence of reinfarction in non-Q-wave infarcts
Antiarrhythmics	These may be used for reperfusion arrhythmias
Oxygen-derived radical scavengers to reduce "reperfusion injury"	Current experimental evidence is divided as to whether these agents are beneficial in myocardial infarct models; a United States clinical trial in patients receiving reperfusion for acute myocardial infarction is under way

ISIS-2 = 2nd International Study of Infarct Survival, TIMI II = Phase II Thrombolysis in Myocardial Infarction [trial]

hypothesis that oxygen radicals generated during reperfusion can irreversibly damage a population of myocytes—"reperfusion injury."[127] This suggests that if oxygen radicals are prevented from forming or are scavenged at reflow, reperfusion injury may be blunted. Considerable controversy surrounds both the concept of reperfusion injury per se and the ability of oxygen-radical scavengers administered during reperfusion to prevent it. Most experimental studies have used canine models of 40 to 120 minutes of coronary artery occlusion followed by reperfusion, with an oxygen-radical scavenger or placebo given at reflow. Some investigators observed a substantial reduction in infarct size in animals treated with free-radical scavengers,[127,128] whereas others noted beneficial effects.[129,130]

Our laboratory also investigated reperfusion injury in anesthetized dogs using an open-chest method.[131] We administered superoxide dismutase and catalase after two hours of coronary artery occlusion and maintained treatment for the initial four hours of reperfusion. Four hours after reflow, we observed no overall reduction in infarct size. A retrospective analysis of these data, however, revealed a small subset of moderately ischemic animals in which acute necrosis was less than in controls given a saline solution. We also observed that treatment with superoxide dismutase and catalase blunted the no-reflow phenomenon; regional myocardial blood flow in the previously ischemic endocardium and midmyocardium was considerably greater in treated animals than in saline controls. Electron microscopy showed that enhanced flow after reperfusion in the enzyme-treated animals was accompanied by the preservation of subendocardial microvasculature. Thus, our data suggest that oxygen-radical scavengers consistently reduced microvascular injury produced by two hours of coronary artery occlusion and four hours of reflow but limited acute myocytic injury in only a small group of dogs. In contrast to results obtained in models of transient (15 minutes) occlusion, superoxide dismutase and catalase had no beneficial effect on the return of cardiac function after prolonged (two hours) ischemia. Thus, oxygen radicals may be important contributors to stunned myocardium induced by brief ischemia but are less important in models of prolonged ischemia followed by reperfusion.

Oxygen-radical scavengers may have another important role. Experimental studies in the surgical literature suggest that oxygen-radical scavengers administered as supplements to standard cardioplegic solutions may enhance tissue preservation.[132] A clinical study is being planned to investigate the effect of oxygen-radical scavengers in patients undergoing cardiopulmonary bypass.

Summary and Conclusions

Although timely reperfusion reduces myocardial infarct size, reperfusion may also have deleterious consequences. For example, contractile function of the previously ischemic tissue can remain depressed or stunned for hours to days following reflow. Oxygen free radicals may play a role in this phenomenon. Various studies have reported that free radical-scavenging agents improve contractile function of myocardium stunned by a brief (15-minute) ischemic episode. Calcium-channel blockers have also been shown to enhance the function of stunned, previously ischemic myocardium, leading to speculation that these two seemingly diverse mechanisms may be interrelated.

Oxygen radicals may also contribute to so-called reperfusion injury, but this hypothesis remains controversial. Administering free radical-scavenging agents during reperfusion does not appear to enhance cardiac function in models of prolonged (two-hour) occlusion followed by reflow, and studies of the effect of these agents on myocardial infarct size have shown mixed results. Oxygen-radical scavengers may protect against the no-reflow problem.

Clinical studies provide evidence that other forms of adjuvant therapy (aspirin, β-blockade) may be beneficial in patients with reperfused infarcts. Ongoing and planned clinical studies are assessing the effects of oxygen-radical scavengers as therapy adjuvant for coronary artery reperfusion following infarction and for cardioplegia in patients undergoing cardiopulmonary bypass procedures.

REFERENCES

1. McFate-Smith W: Epidemiology of congestive heart failure. Am J Cardiol 1985; 55:3A-8A

2. McKee PA, Castelli WP, McNamara PM, et al: The natural history of congestive heart failure: The Framingham study. N Engl J Med 1971; 285:1441-1446

3. Francis GS: Development of arrhythmias in the patient with congestive heart failure: Pathophysiology, prevalence, and prognosis. Am J Cardiol 1986; 57:3B-7B

4. Cohn JN, Archibald DG, Ziesche S, et al: Effect of vasodilator therapy on mortality in chronic congestive heart failure—Results of a Veterans Administration Cooperative Study. N Engl J Med 1986; 314:1547-1552

5. CONSENSUS Trial Study Group: Effect of enalapril on mortality in severe congestive heart failure: Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med 1987; 316:1429-1435

6. Gheorghiade M, St Clair J, St Clair C, Beller GA: Hemodynamic effects of intravenous digoxin in patients with severe heart failure initially treated with diuretics and vasodilators. J Am Coll Cardiol 1987; 9:849-857

7. Mancini D, LeJemtel T, Sonnenblick E: Intravenous use of amrinone for the treatment of the failing heart. Am J Cardiol 1985; 56:8B-14B

8. Swedberg K, Hjalmarson A, Waagstein F, Wallentin I: Prolongation of survival in congestive cardiomyopathy by β-receptor blockade. Lancet 1979; 1:1374-1376

9. Chakko CS, Gheorghiade M: Ventricular arrhythmias and severe heart failure: Incidence, significance, and effectiveness of antiarrhythmic therapy. Am Heart J 1985; 109:497-504

10. Stevenson LW, Laks H, Terasaki PI, Kahan BD, Drinkwater DC: Cardiac transplantation—Selection, immunosuppression, and survival. West J Med 1988; 149:572-582

11. Watanabe AM: Recent advances in knowledge about β-adrenergic receptors: Application to clinical cardiology. J Am Coll Cardiol 1983; 1:82-89

12. Linderer T, Biamino G, Bruggermann T, et al: Hemodynamic effects of forskolin, a new drug with combined positive inotropic and vasodilating properties (Abstr). J Am Coll Cardiol 1984; 3:562

13. Lefkowitz RJ, Stadel JM, Caron MG: Adenylate cyclase-coupled β-adrenergic receptors: Structure and mechanism of activation and desensitization. Annu Rev Biochem 1983; 52:159-186

14. Langer SZ: Presynaptic regulation of catecholamine release. Biochem Pharmacol 1974; 23:1793-1800

15. Bruckner R, Meyer W, Mügge A, Schmitz W, Scholtz H: α-Adrenoceptor-mediated positive inotropic effect on phenylephrine in isolated human ventricular myocardium. Eur J Pharmacol 1984; 99:345-347

16. Colucci WS: α-Adrenergic receptors in cardiovascular medicine, chap 2, *In* Haft JI, Karliner JS (Eds): Receptor Science in Cardiology. Mount Kisco, NY, Futura Publishing, 1984, pp 43-80

17. Goldberg MR, Robertson D: Evidence for the existence of vascular α-adrenergic receptors in humans. Hypertension 1984; 6:551-556

18. Goldberg LI, Rajfer SI: Dopamine receptors—Applications in clinical cardiology. Circulation 1985; 72:245-248

19. Renard M, Jacobs P, Dechamps P, Dresse A, Bernard R: Hemodynamic and clinical response to three-day infusion of sulmazol (AR-L 115 BS) in severe congestive heart failure. Chest 1983; 84:408-413

20. Smith TW, Antman EM, Friedman PL, Blatt CM, Marsh JD: Digitalis glycosides: Mechanisms and manifestations of toxicity—Part III. Prog Cardiovasc Dis 1984; 27:21-56 (670 ref)

21. Leier CV, Heban PT, Huss P, Bush CA, Lewis RP: Comparative systemic and regional hemodynamic effects of dopamine and dobutamine in patients with cardiomyopathic heart failure. Circulation 1978; 58:466-475

22. Dell'Italia LJ, Starling MD, Blumhardt R, Lasher JC, O'Rourke RA: Comparative effects of volume loading, dobutamine, and nitroprusside in patients with predominant right ventricular infarction. Circulation 1985; 72:1327-1335

23. Goldstein RA, Passamani ER, Roberts R: A comparison of digoxin and dobutamine in patients with acute infarction and cardiac failure. N Engl J Med 1980; 303:846-850

24. DeMarco T, Kwasman M, Lau D, Chatterjee K: Dopexamine hydrochloride in chronic congestive heart failure with improved cardiac performance without increased metabolic cost. Am J Cardiol 1988; 62:57C-62C

25. Fennell WH, Taylor AA, Young JB, et al: Propylbutyldopamine: Hemodynamic effects in conscious dogs, normal human volunteers and patients with heart failure. Circulation 1983; 67:829-836

26. Francis GS, Parks R, Cohn JN: The effects of bromocriptine in patients with congestive heart failure. Am Heart J 1983; 106:100-106

27. Leon CA, Suarez JM, Aranoff RD, et al: Fenoldopam: Efficacy of a new orally active dopamine analog in heart failure (Abstr). Circulation 1984; 70(Suppl II):307

28. Rajfer SI, Rossen JD, Douglas FL, Goldberg LI, Karrison T: Effects of long-term therapy with oral ibopamine on resting hemodynamics and exercise capacity in patients with heart failure: Relationship to the generation of *N*-methyldopamine and to plasma norepinephrine levels. Circulation 1986; 73:740-748

29. Rajfer SI, Anton AH, Rossen JD, Goldberg LI: Beneficial hemodynamic effects of oral levodopa in heart failure: Relationship to the generation of dopamine. N Engl J Med 1984; 310:1357-1362

30. Thompson MJ, Huss P, Unverferth DV, Fasola A, Leier CV: Hemodynamic effects of intravenous butopamine in congestive heart failure. Clin Pharmacol Ther 1980; 28:324-334

31. Kino M, Hirota Y, Yamamoto S, et al: Cardiovascular effects of a newly synthesized cardiotonic agent (TA-064) on normal and diseased hearts. Am J Cardiol 1983; 51:802-810

32. Sharma B, Goodwin JF: Beneficial effect of salbutamol on cardiac function in severe congestive cardiomyopathy: Effect on systolic and diastolic function of the left ventricle. Circulation 1978; 58:449-460

33. Awan NA, Needham KE, Evenson MK, et al: Therapeutic efficacy of oral pirbuterol in severe chronic congestive heart failure—Acute hemodynamic and long-term ambulatory evaluation. Am Heart J 1981; 102(Pt 2):555-563

34. Wahr DW, Swedberg K, Rabbino M, et al: Intravenous and oral prenalterol in congestive heart failure—Effects on systemic and coronary hemodynamics and myocardial catecholamine balance. Am J Med 1984; 76:999-1005

35. Bhataia JSS, Swedberg K, Chatterjee K: Acute hemodynamic and metabolic effects of ICI 118,587 (Corwin), a selective partial β-agonist, in patients with dilated cardiomyopathy. Am Heart J 1986; 111:692-696

36. Ludmer PL, Wright RF, Arnold JM, Ganz P, Braunwald E: Separation of the direct myocardial and vasodilator actions of milrinone administered by an intracoronary infusion technique. Circulation 1986; 73:130-137

37. Kereiakes D, Chatterjee K, Parmley WW, et al: Intravenous and oral MDL 17,043 (a new inotrope-vasodilator agent) in congestive heart failure: Hemodynamic and clinical evaluation in 38 patients. J Am Coll Cardiol 1984; 4:884-889

38. Petein M, Levine B, Cohn JN: Hemodynamic effects of a new inotropic agent, piroximone (MDL 19,205) in patients with chronic heart failure. J Am Coll Cardiol 1984; 4:364-371

39. Daly PA, Chatterjee K, Viquerat CE, et al: RO13-6438, a new inotrope-vasodilator: Systemic and coronary hemodynamic effects in congestive heart failure. Am J Cardiol 1985; 55(Pt 1):1539-1544

40. Kereiakes DJ, Viquerat C, Lanzer P, et al: Mechanisms of improved left ventricular function following intravenous MDL 17,043 in patients with severe chronic heart failure. Am Heart J 1984; 108:1278-1284

41. Unverferth DV, Magorien RD, Lewis RP, Leier CV: Long-term benefit of dobutamine in patients with congestive cardiomyopathy. Am Heart J 1980; 100:622-630

42. Cantelli I, Lolli C, Bomba E, et al: Sustained oral treatment with ibopamine in patients with chronic congestive heart failure. Curr Ther Res 1986; 39:900-910

43. Zipperle G, Butzer F, Dieterich HA, Heinrich F: A double-blind dose-response comparison of oral enoximone and placebo for congestive heart failure. Am J Cardiol 1987; 60:72C-74C

44. DiBianco R, Shabetai R, Kastuk W, Moran J, Schlant RC, Wright R, for the Milrinone Multicenter Trial Group: A comparison of oral milrinone, digoxin, and their combination in the treatment of patients with chronic heart failure. N Engl J Med 1989; 320:677-683

45. Dean JW, Lab MJ: Arrhythmia in heart failure: Role of mechanically induced changes in electrophysiology. Lancet 1989; 1:1309-1312

46. Mullins LJ: The generation of electrical currents in cardiac fibers by sodium-calcium exchange. Am J Physiol 1979; 263:C103-C110

47. Dargie HJ, Cleland JGF, Leckie BJ, Inglis CG, East BW, Ford I: Relation of arrhythmias and electrolyte abnormalities to survival in patients with severe chronic heart failure. Circulation 1987; 75(Suppl IV):98-107

48. Cleland JGF, Dargie HJ, Hodsman GP, et al: Captopril in heart failure: A double blind controlled trial. Br Heart J 1984; 52:530-535

49. Webster MWI, Fitzpatrick A, Nicholls G, Ikram H, Wells JE: Effect of enalapril on ventricular arrhythmias in congestive heart failure. Am J Cardiol 1985; 56:566-569

50. Thomas JA, Marks BH: Plasma norepinephrine in congestive heart failure. Am J Cardiol 1978; 41:233-243

51. Francis GS, Goldsmith SR, Levine TB, Olivari MT, Cohn JN: The neurohumoral axis in congestive heart failure. Ann Intern Med 1984; 101:370-377

52. Cohn JN, Levine TB, Olivari MT, et al: Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. N Engl J Med 1984; 311:819-823

53. Goldberg LI: Dopamine—Clinical uses of an endogenous catecholamine. N Engl J Med 1974;291:707-710

54. Sonnenblick EH, Frishman WH, LeJemtel TH: Dobutamine: A new synthetic cardioactive sympathetic amine. N Engl J Med 1979; 300:17-22

55. Moss AJ, Davis HT, Conrad DL, De Camilla JJ, Oderoff CL: Digitalis associated with cardiac mortality after myocardial infarction. Circulation 1981; 64:1150-1156

56. Yusuf S, Wittes J, Bailey K, Furberg C: Digitalis—A new controversy regarding an old drug. Circulation 1986; 73:14-18

57. Cohn JN, Ziesche S, Archibald DG, and the VA Cooperative Study Group: Quantitative exercise tolerance as a predictor of mortality in congestive heart failure: The V-HeFT study (Abstr). Circulation 1986; 74(Suppl II):447

58. Velebit V, Podrid P, Lown B, Cohen BH, Graboys TB: Aggravation and provocation of ventricular arrhythmias by antiarrhythmic drugs. Circulation 1982; 65:886-894

59. Woosley RL: Pharmacokinetics and pharmacodynamics of antiarrhythmic agents in patients with congestive heart failure. Am Heart J 1987; 114:1280-1291

60. Hohnloser SH, Raeder EA, Podrid PJ, Graboys TB, Lown B: Predictors of antiarrhythmic drug efficacy in patients with malignant ventricular tachyarrhythmias. Am Heart J 1987; 114:1-7

61. Lampert S, Lown B, Graboys TB, Podrid PJ, Blatt CM: Determinants of survival in patients with malignant ventricular arrhythmias associated with coronary artery disease. Am J Cardiol 1988; 61:791-797

62. Rae AP, Spielman SR, Kutelek SP, Kay HR, Horwitz LN: Electrophysiologic assessment of antiarrhythmic drug efficacy for ventricular tachyarrhythmias associated with dilated cardiomyopathy. Am J Cardiol 1987; 59:291-295

63. Brodsky MA, Allen BJ, Baron D, et al: Enhanced survival in patients with heart failure and life-threatening ventricular tachyarrhythmias. Am Heart J 1986; 112:1166-1172

64. Minardo JD, Heger JJ, Miles WM, Zipes DP, Prystowsky EN: Clinical characteristics of patients with ventricular fibrillation during antiarrhythmic drug therapy. N Engl J Med 1988; 319:257-262

65. Francis GS: Should asymptomatic ventricular arrhythmias in patients with congestive heart failure be treated with antiarrhythmic drugs? Introduction. J Am Coll Cardiol 1988; 12:274-276

66. Stamato NJ, O'Connell JB, Murdock DK, Moran JF, Loeb HS, Scanlon PJ: The response of patients with complex ventricular arrhythmias secondary to dilated cardiomyopathy to programmed electrical stimulation. Am Heart J 1986; 112:505-508

67. Simonton CA, Daly PA, Kereiakes D, Modin G, Chatterjee K: Survival in severe left ventricular failure treated with the new nonglycosidic, nonsympathomimetic oral inotropic agents. Chest 1987; 92:118-123

68. Neri R, Mestroni L, Salvi A, Pandullo C, Camerini F: Ventricular arrhythmias in dilated cardiomyopathy: Efficacy of amiodarone. Am Heart J 1987; 113:707-715

69. Nicklas JM, Mickelson JK, Das SK, Morady F, Schork MA, Pitt B: Prospective, randomized, double-blind, placebo-controlled trial of low dose amiodarone in patients with severe heart failure and frequent ventricular ectopy (Abstr). Circulation 1988; 78(Suppl II):27

70. Kannel MB, Sorlie P, McNamara PM: Prognosis after initial myocardial infarction: The Framingham study. Am J Cardiol 1979; 44:53-59

71. Serruys PW, Simoons ML, Suryapranata H, et al: Preservation of global and regional left ventricular function after early thrombolysis in acute myocardial infarction. J Am Coll Cardiol 1986; 7:729-742

72. Hammermeister KE, De Rouen TA, Dodge HT: Variables predictive of survival in patients with coronary disease. Circulation 1979; 59:421-430

73. White HD, Norris RM, Brown MA, Brandt PWT, Whitlock RML, Wild CJ:

Left ventricular end-systolic volume as the major determinant of survival after recovery of function from myocardial infarction. Circulation 1987; 76:44-51

74. Klein MD, Herman MV, Gorlin R: A hemodynamic study of left ventricular aneurysm. Circulation 1967; 35:614-630

75. Kitamura S, Kay JH, Krohn BG, Magidson O, Dunne EF: Geometric and functional abnormalities of the left ventricle with a chronic localized non-contractile area. Am J Cardiol 1973; 31:701-707

76. Hutchins GM, Bulkley BH: Infarct expansion versus extension: Two different complications of acute myocardial infarction. Am J Cardiol 1978; 41:1127-1132

77. Eaton LW, Weiss JL, Bulkley BH, Garrison JB, Weisfeldt ML: Regional cardiac dilatation after acute myocardial infarction: Recognition by two-dimensional echocardiography. N Engl J Med 1979; 300:57-62

78. Erlebacher JA, Weiss JL, Eaton LW, Kallman C, Weisfeldt ML, Bulkley BH: Late effects of acute infarct dilation on heart size: A two-dimensional echocardiographic study. Am J Cardiol 1982; 49:1120-1126

79. Weisman HF, Bush DE, Mannisi JA, Bulkley BH: Global cardiac remodeling after acute myocardial infarction: A study in the rat model. J Am Coll Cardiol 1985; 5:1355-1362

80. Nolan SE, Mannisi JA, Bush DE, Healy B, Weisman HF: Increased afterload aggravates infarct expansion after acute myocardial infarction. J Am Coll Cardiol 1988; 12:1318-1325

81. Christensen DJ, Ford M, Reading J, Castle CH: Effect of hypertension on myocardial rupture after acute myocardial infarction. Chest 1977; 72:618-622

82. Karam R, Wicker P, Sen S, Healy B: Coronary circulation in post-infarction hypertrophy (Abstr). Circulation 1988; 78(Suppl II):170

83. Hammerman H, Kloner RA, Hale S, Schoen FJ, Braunwald E: Dose-dependent effects of short-term methylprednisone on myocardial infarct extent, scar formation, and ventricular function. Circulation 1983; 68:446-452

84. McKay RG, Pfeffer MA, Pasternak RC, et al: Left ventricular remodeling after myocardial infarction: A corollary to infarct expansion. Circulation 1986; 74:693-702

85. Warren SE, Royal HD, Markis JE, Grossman W, McKay RG: Time course of left ventricular dilation after myocardial infarction: Influence of infarct-related artery and success of coronary thrombolysis. J Am Coll Cardiol 1988; 11:12-19

86. Jeremy RW, Hackworthy RA, Bautovich G, Hutton BF, Harris PJ: Infarct artery perfusion and changes in left ventricular volume in the month after acute myocardial infarction. J Am Coll Cardiol 1987; 9:989-995

87. Pfeffer JM, Pfeffer MA, Braunwald E: Influence of chronic captopril therapy on the infarcted left ventricle of the rat. Circ Res 1985; 57:84-95

88. Pfeffer MA, Pfeffer JM, Steinberg C, Finn P: Survival after an experimental myocardial infarction: Beneficial effects of long-term therapy with captopril. Circulation 1985; 72:406-412

89. Pfeffer MA, Lamas GA, Vaughn DE, Parisi AF, Braunwald E: Effect of captopril on progressive ventricular dilatation after anterior myocardial infarction. N Engl J Med 1988; 319:80-86

90. Sharpe N, Murphy J, Smith H, Hannan S: Treatment of patients with symptomless left ventricular dysfunction after myocardial infarction. Lancet 1988; 1:255-259

91. Herlitz J, Elmfeldt D, Holmberg S, et al: Göteborg Metoprolol Trial: Mortality and causes of death. Am J Cardiol 1984; 53:9D-14D

92. Yusuf S: Interventions that potentially limit myocardial infarct size: Overview of clinical trials. Am J Cardiol 1987; 60:11A-17A

93. Braunwald E, Kloner RA: Perspective: Myocardial reperfusion—A double-edged sword? J Clin Invest 1985; 76:1713-1719

94. Reimer KA, Lowe JE, Rasmussen MM, Jennings RB: The wavefront phenomenon of ischemic cell death—Myocardial infarct size vs duration of coronary occlusion in dogs. Circulation 1977; 56:786-793

95. Guerci AD, Gerstenblith G, Brinker JA, et al: A randomized trial of intravenous tissue plasminogen activator for acute myocardial infarction with subsequent randomization to elective coronary angioplasty. N Engl J Med 1987; 317:1613-1618

96. Franzosi MG, Mauri F, Pampallona S, et al: The GISSI study: Further analysis—Italian Group for the Study of Streptokinase in Myocardial Infarction. Circulation 1987; 76(Suppl II):52-56

97. Hale SL, Kloner RA: Left ventricular topographic alterations in completely healed rat infarct caused by early and late coronary artery reperfusion. Am Heart J 1988; 116:1508-1513

98. Arnold JMO, Antman EM, Przyklenk K, et al: Differential effects of reperfusion on incidence of ventricular arrhythmias and recovery of ventricular function at 4 days following coronary occlusion. Am Heart J 1987; 113:1055-1065

99. 2nd International Study of Infarct Survival Collaborative Group: Randomized trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. Lancet 1988; 2:349-360

100. Kennedy JW, Ritchie JL, Davis KB, Fritz JK: Western Washington randomized trial of intracoronary streptokinase in acute myocardial infarction. N Engl J Med 1983; 309:1477-1482

101. Hammond B, Hess ML: The oxygen free radical system: Potential mediator of myocardial injury. J Am Coll Cardiol 1985; 6:215-220

102. Simpson PJ, Mickelson JK, Lucchesi BR: Free radical scavengers in myocardial ischemia. Fed Proc 1987; 46:2413-2421

103. Whittaker P, Kloner RA, Przyklenk K: In vivo damage by exogenous oxygen radicals mimics ischemia/reperfusion injury (Abstr). Circulation 1988; 78(Suppl II):30

104. Blaustein AS, Schine L, Brooks WW, Fanburg BL, Bing OHL: Influence of exogenously generated oxidant species on myocardial function. Am J Physiol 1986; 19:H595-H599

105. Bolli R, Patel BS, Jerondi MO, Lai EK, McCay PB: Demonstration of free radical generation in 'stunned' myocardium of intact dogs with the use of the spin trap α-phenyl *N*-tert-butyl nitrone. J Clin Invest 1988; 82:476-485

106. McCord JM: Oxygen-derived free radicals in postischemic tissue injury. N Engl J Med 1985; 312:159-163

107. Eddy LJ, Stewart JR, Jones HP, Engessen TP, McCord JM, Downey JM: Free radical-producing enzyme, xanthine oxidase, is undetectable in human hearts. Am J Physiol 1987; 253:H709-H711

108. Kloner RA, Alker KJ, Campbell C, Figures G, Eisenhower A, Hale S: Does tissue-type plasminogen activator have direct beneficial effects on myocardium independent of its ability to lyse intracoronary thrombi? Circulation 1989; 79:1125-1136

109. Westlin W, Mullane K: Does captopril attenuate reperfusion-induced myocardial dysfunction by scavenging free radicals? Circulation 1988; 77(Suppl I):30-39

110. Boveris A: Mitochondrial production of superoxide radical and hydrogen peroxide. Adv Exp Med Biol 1977; 78:67-82

111. Braunwald E, Kloner RA: The stunned myocardium—Prolonged, post-ischemic ventricular dysfunction. Circulation 1982; 66:1146-1149

112. Przyklenk K, Kloner RA: Superoxide dismutase plus catalase improve contractile function in the canine model of 'stunned myocardium.' Circ Res 1986; 58:148-156

113. Bolli R: Oxygen-derived free radicals and postischemic myocardial dysfunction ('stunned myocardium'). J Am Coll Cardiol 1988; 12:239-249

114. Engler RL, Covell JW: Granulocytes cause reperfusion ventricular dysfunction after 15-minute ischemia in the dog. Circ Res 1987; 61:20-28

115. Jeremy RW, Becker LC: Neutrophil depletion does not prevent myocardial dysfunction after brief coronary occlusion. J Am Coll Cardiol 1989; 13:1155-1163

116. O'Neill PG, Charlat ML, Michael LH, Roberts R, Bolli R: Influence of neutrophil depletion on myocardial function and flow after reversible ischemia. Am J Physiol 1989; 256:H341-H351

117. DeBoer LVW, Ingwall JS, Kloner RA, Braunwald E: Prolonged derangements of canine myocardial purine metabolism following a brief coronary artery occlusion not associated with anatomic evidence of necrosis. Proc Natl Acad Sci USA 1980; 77:5471-5475

118. Go LO, Murry CE, Richard VJ, Weischedel OR, Reimer KA, Jennings RB: Myocardial neutrophil accumulation during reperfusion after reversible or irreversible ischemic injury. Am J Physiol 1988; 255:H1188-H1198

119. Przyklenk K, Ghafari GB, Eitzman DT, Kloner RA: Nifedipine administered after reperfusion ablates contractile dysfunction of postischemic 'stunned' myocardium. J Am Coll Cardiol 1988; 13:1176-1183

120. Przyklenk K, Kloner RA: Effect of verapamil on postischemic 'stunned' myocardium: Importance of timing of treatment. J Am Coll Cardiol 1988; 11:614-623

121. Przyklenk K, Kloner RA: Acute effects of hydralazine and enalapril on contractile function of postischemic 'stunned myocardium.' Am J Cardiol 1987; 60:934-936

122. Reimer KA, Jennings RB: Verapamil in two reperfusion models of myocardial infarction—Temporary protection of severely ischemic myocardium without limitation of ultimate infarct size. Lab Invest 1984; 51:655-666

123. Lo HM, Kloner RA, Braunwald E: Effect of intracoronary verapamil on infarct size in ischemic, reperfused canine heart: The critical importance of the timing of treatment. Am J Cardiol 1985; 56:672-677

124. Hammerman H, Kloner RA, Briggs LL, Braunwald E: Enhancement of salvage of reperfused myocardium by early β-adrenergic blockade (timolol). J Am Coll Cardiol 1984; 3:1438-1443

125. Reimer KA, Jennings RB: Decreasing myocardial energy utilization, chap 17, *In* Wagner GS (Ed): Myocardial Infarction: Measurement and Intervention. The Hague, Netherlands, Martinus Nijhoff, 1982, pp 397-414

126. Thrombolysis in Myocardial Infarction (TIMI) Study Group: Comparison of invasive and conservative strategies after treatment with intravenous tissue plasminogen activator in acute myocardial infarction—Results of the Thrombolysis in Myocardial Infarction (TIMI) Phase II trial. N Engl J Med 1989; 320:618-627

127. Flaherty JT, Weisfeldt ML: Reperfusion injury. Free Radic Biol Med 1988; 5:409-419

128. Ambrosio G, Becker LC, Hutchins GM, Weisman HF, Weisfeldt ML: Reduction in experimental infarct size by recombinant human superoxide dismutase: Insights into the pathophysiology of reperfusion injury. Circulation 1986; 74:1424-1433

129. Uraizee A, Reimer KA, Murry CE, Jennings RB: Failure of superoxide dismutase to limit size of myocardial infarction after 40 minutes of ischemia and 4 days of reperfusion in dogs. Circulation 1987; 75:1237-1248

130. Nejima J, Knight DR, Fallon JT, et al: Superoxide dismutase reduces reperfusion arrhythmias but fails to salvage regional function or myocardium at risk in conscious dogs. Circulation 1989; 79:143-153

131. Przyklenk K, Kloner RA: 'Reperfusion injury' by oxygen-derived free radicals? Effect of superoxide dismutase plus catalase, given at the time of reperfusion, on myocardial infarct size, contractile function, coronary microvasculature, and regional myocardial blood flow. Circ Res 1989; 64:86-96

132. Greenfield DT, Greenfield LJ, Hess ML: Enhancement of crystalloid cardioplegic protection against global nonthermic ischemia by superoxide dismutase plus catalase but not diltiazem in isolated working rat heart. J Thorac Cardiovasc Surg 1988; 95:799-813